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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/001,934	Nagy et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-116* is/are pending in the application.

4a) Of the above, claim(s) *39-42, 44-54, 57, 58, 64, 65, and 96-116* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-23, 30-38, 43, 55, 56, 59-63, 66-81, and 88-95* is/are rejected.

7) ☒ Claim(s) *24-29 and 82-87* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election of Group I, claims 1-38, 43, 55, 56, 59-63, 66-95 and 109-115 in the response of December 9, 2002 in addition to B-cell non-Hodgkin's lymphoma, the derived cell line KARPAS-422, the clone GPC-8-27-41, and multiple sclerosis as a disorder recited in claim 53, 54, 106, and 107. Acknowledgment is also made of applicant's election of Group I, claims 1-38, 43, 55, 56, 59-63, 66-95, drawn to a composition, in the response of April 29, 2003. All the elections were made with traverse. The traversal is on the grounds that it would not be undue burden on the examiner to search the products of Group I and II. Group I is, drawn to compositions comprising a polypeptide comprising an antibody-based antigen-binding domain which specifically binds to an antigen expressed on the surface of a human cell, wherein treating said cell with said composition results in the killing of said cell without cytotoxic entities or immunological mechanisms; kits thereof; and, methods for conducting a business comprising licensing, jointly developing, selling the rights to sell and marketing said composition. Group II is drawn to a nucleic acid comprising a protein coding sequence of the antigen-binding domain of the polypeptide of Group I or a multivalent polypeptide, thereof, vectors and host cells harboring said nucleic acid, methods for recombinantly producing a multivalent polypeptide. Protein products and nucleic acid products are made in entirely different ways and have different uses. The examination of both products would increase the search burden significantly as the literature search, particularly important in this are, is not coextensive. Applicant points out that Groups III and IV are method claims which depend upon Groups I and II and quotes the MPEP to state that process claims which depend from or otherwise include all the limitations of an allowable product claim should be rejoined after allowance of the product claim. Applicant alleges that claims 1-11, 17-21, 24, 26, 28, 30-50, 52, 55, 57-66, 68-79, 82, 84, 88-105, 108-114 and 116 are generic linking claims linking elected and non-elected species. The examiner is in disagreement with this statement. The recited claims are generic, but they are not linking claims. However, this point is moot as the restriction requirement of Paper No. 10 stated, "Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent

form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141". Applicant also argues in the response of December 9, 2002 that the separation of diseases in species (c) is unwarranted as the examination of all the diseases would not be undue burden on the examiner. Applicant quotes the MPEP in stating "If the members of a Markush Group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, then the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions"
It is noted that applicant is mis-quoting the MPEP. The correct statement is:
If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all **the members of the Markush group in** the claim on the merits, even though they are directed to independent and distinct inventions.

Further, there are 21 species of disorders recited in claims 53-54 which range from insulin-dependent diabetes to graft versus host disease to thyroiditis. A search for all these diseases would not be co-extensive in the literature, and thus would result in a serious burden on the examiner. It is noted that the currently elected claims do not include a disorder. Thus, applicant's argument is moot.

Applicant has also traversed the restriction requirement of Paper No. 14, stating that the inclusion of claims drawn to methods of conducing a pharmaceutical business would not be an undue burden on the examiner. It is noted that these methods are completely different from the recited method claims, and that completely different issues of patentability apply to such claims, therefore it can be concluded that the inclusion of the claims of Group II (Paper No. 14) would be an undue burden

Applicant request the examination of the species of GRANTA-519 cells in addition to the elected species of KARPAS-422 cells, as both cell lines are derived from B-cell non-Hodgkin's lyphoma. This is persuasive. KARPAS-422 and GRANTA-519 cells will be examined as species of claim 13. Additionally, after review and reconsideration, claim 16, drawn to LG2 cells and PRIESS cells will also be examined.

2. Claims 1-116 are pending. Claims 39-42, 44-54, 57, 58, 64, 65 and 96-116, drawn to non elected inventions, are withdrawn from consideration. Claims 1-38, 43, 55, 56, 59-64 and 66-95 are examined on the merits.

Claim Objections

3. Claims 62 and 63 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 62 and 63 are drawn to the compositions of any one of claims 1-6 operably linked to a cytotoxic, or immunogenic agent, respectively. Claims 1-5 all recite the limitation, "neither cytotoxic nor immunological mechanisms are need for cell killing". The inclusion of cytotoxic or immunogenic agents in claims 62 and 63 are contrary to the limitations of claims 1-5. For purpose of examination, claims 62 and 63 will be read as independent claims.

4. Claim 70 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 70 is drawn in part to a composition of claim 67, wherein said antigen-binding domain binds to HLA-DR. Claim 67 includes the limitation of binding to the HLA-DR antigen.

5. Claims 24-29 and 82-87 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 13-16, 22, 23, 33, 67, 80 and 81 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-16 are vague and indefinite in the recitation of GRANTA-519. KARPAS-422, LG2 and PRIESS as the only means of identifying the cell lines which characterize the binding of claimed antibody. The use of laboratory designations only to identify a cell line renders the claim vague and indefinite as other laboratories can use different designations to identify the same cell line, or other laboratories can use the same designation to identify a totally different cell line. Amendment of the claim to incorporate a deposit accession number would overcome this rejection.

Claims 22, 23, 67, 80, 81 are rendered vague and indefinite in reliance of the term MS-GPC-8-27-41 to identify the clone on which is based the variable chain region of the claimed antibody. MS-GPC-8-27-41 is a laboratory designation coined by the inventor. Amendment of the claims to incorporate sequence identifiers or deposit accession numbers would overcome this rejection.

Claim 33 is rendered vague and indefinite in the recitation of "a mini-antibody fragment". Without a definition, the metes and bounds of what constitutes a "mini-antibody fragment" cannot be determined.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 17 and 38 and rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. .

Claim 38 is drawn to the composition of claim 3 or 4, wherein the antigen-binding sites are cross-linked to a polymer. Claims 3 and 4 are drawn to a plurality of antigen binding domains which specifically bind to human HLA-DR. The antigen-binding sites of an antibody are termed "paratopes". It is well known in the art that a paratope minimally comprises a CDR region, and in some cases comprises additional residues in the variable chain regions (Amit et al Science Vol 233 747-753 1986). When given the broadest reasonable interpretation, claim 38 can be read as minimally comprising only the CDR regions of the antibody, which are cross-linked to a polymer. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor of the CDRs as a result of the cross-linking to the polymer, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that a polymer upon which CDRs from the heavy and light chain variable regions of an antibody are attached in unspecified order would have the required binding function. The specification provides no direction or guidance regarding how to produce CDR regions cross linked to a polymer which will retain the binding activity of the variable regions from which they were derived. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. One of skill in the art would neither expect nor predict the appropriate functioning of the antigen-binding

regions cross linked to a polymer as claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to make and use the claimed invention.

10. Claims 13-16, 22, 23, 67, 80 and 81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(A)As drawn to specific cell lines

Claims 13-16 are drawn to specific cell lines. It is unclear whether the exact cell lines possessing the identical properties of KARPAS-422. GRANTA-519, LG2 and PRIESS are known and are publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. It is unclear that one of skill in the art could derive cell lines identical to those claimed.

Because one of ordinary skill in the art could not be assured of the availability to practice the invention as claimed in the absence of the availability of the claimed cell lines, a suitable deposit of the cell line for patent purposes, evidence of public availability of the cell lines, or evidence of reproducibility without undue experimentation of the claimed cell lines is required.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(C) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited cell lines are the same as those described in the specification as filed, stating that the deposited cell lines were the same as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

(B)As drawn to clones of unknown identity

Claims 22, 23, , 67, 80 and 81 are dependent upon the identity of the clone MS-GPC-8-27-41. As this is a laboratory designation, the amino acid sequence or polynucleotide sequence of which is unknown, one of skill in the art could not practice the claimed invention without a sequence disclosure or a deposit of a cell line comprising said clone.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 62 is rejected under 35 U.S.C. 102(b) as being anticipated by Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular foundations of Oncology, 1991, pages 95-134). Claim 62 is drawn to a composition comprising a polypeptide comprising antibody-based antigen-binding domain with binding specificity for an antigen expressed on the surface of a human cell, wherein said polypeptide further comprises said polypeptide linked to a cytotoxic agent. Schlom reviews immunotoxins comprising antibodies which bind to the surface of a human cell linked to cytotoxic agents (pages 107-108, under the heading "Drug and Toxin mAb Conjugates).

13. Claim 63 is rejected under 35 U.S.C. 102(b) as being anticipated by the abstract of George et al (Journal of Immunology, 1988, Vol. 141, pp. 2168-2174).

Claim 63 is drawn to a composition comprising a polypeptide comprising antibody-based antigen-binding domain with binding specificity for an antigen expressed on the surface of a human cell, wherein said polypeptide further comprises said polypeptide linked to a immunogenic agent.

The abstract of George et al discloses Bcl1-IgM antibody linked to the immunogenic agent KLH. The antibody has binding specificity for a T-cell receptor and thus fulfills the specific embodiment of binding specificity expressed in the surface of a cell.

14. Claims 2, 7-11, 18-20, 30-36, 55, 56, 66, 71-78 and 88-95 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and Molecular Immunology (text), 1991, page 165).

Claim 2 is drawn to a composition including a polypeptide comprising an antibody-based antigen-binding domain which binds to human HLA-DR with a Kd of 1 muM or less, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. Claim 7 is drawn to the composition of any of claims 1-6, wherein the multivalent polypeptide has an EC 50 for killing transformed cells at least 5-fold lower than the EC.50 for killing normal cells. Claim 8 is drawn to the composition of any of claims 1-6, wherein the multivalent polypeptide has an EC.50 for killing activated cells at least 5-fold lower than the EC.50 for killing inactivated cells. Claim 9 is drawn to the composition of any of claims 1-6, wherein the multivalent polypeptide has an EC.50 of 50 nM or less for killing transformed cells. Claim 10 is drawn to the composition of any of claims 1-6, wherein the multivalent polypeptide has an EC.50 for killing lymphoid tumor cells of 10 nM or less. Claim 11 is drawn to he composition of any of claims 1-6, wherein the multivalent polypeptide kills activated lymphoid cells. Claim 12 embodies the composition of claim 11, wherein said activated lymphoid cells are B cell non-Hodgkin lymphoma. Claim 16 is drawn to the composition of any of claims 1-6, wherein the multivalent polypeptide has an EC.50 of 10 nM or less for killing cells from at least one B cell lymphoblastoid cell line selected from the group consisting of LG2 and PRIESS. Claim 17 is drawn to the composition of any of claims 1-6, wherein said cells are non-lymphoid cells that express MHC class II molecules. Claim 18 is drawn to the composition of any of claims 1-6, wherein said antigen-binding domain binds to the

.beta.-chain of HLA-DR. Claim 19 is drawn to he composition of claim 18, wherein said antigen-binding domain binds to the first domain of the .beta.-chain of HLA-DR. Claim 20 is drawn to the composition of any of claims 1-6, wherein said antigen-binding domain binds to one or more HLA-DR types selected from the group consisting of DR1-0101, DR2-15021, DR3-0301, DR4Dw4-0401, DR4Dw10-0402, DR4Dw14-0404, DR6-1302, DR6-1401, DR8-8031, DR9-9012, DRw53-B4*0101 and Drw52-B3*0101. Claim 21 is drawn to the composition of claim 20, wherein said antigen-binding domain binds to at least 5 different of said HLA-DR types. Claim 30 is drawn to the composition of any of claims 1-6, wherein the mechanism of said killing involves an innate pre-programmed process of said cell. Claim 31 embodies the composition of claim 30, wherein said killing is non-apoptotic. Claim 32 embodies the composition of claim 30, wherein said killing is dependent on the action of non-caspase proteases, and/or wherein said killing cannot be inhibited by zVAD-fink or zDEVD-fnk. Claim 33 is drawn to the composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide including at least a F(ab').2 antibody fragment Claim 34 is drawn to the composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least two monovalent antibody fragments selected from Fv, scFv, dsFv and Fab fragments, and further comprises a cross-linking moiety or moieties. Claim 35 is drawn to the composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least one full antibody selected from the antibodies of classes IgG.sub.1, 2a, 2b, 3, 4, IgA, and IgM. Claim 36 is drawn to the composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed prior to binding to a cell. Claim 43 is drawn to the composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent. Claim 55 is drawn to a diagnostic composition including the composition of any of claims 1-6.

Claim 66 is drawn to composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a K.sub.d of 1 .mu.M or less, wherein treating cells expressing said antigen with

said polypeptide causes or leads to suppression of an immune response. Claim 70 embodies the composition of any of claims 67, 68 or 69, wherein said antigen-binding domain binds to HLA-DR. Claim 71 embodies he composition of any of claims 66-69 wherein said antigen-binding domain binds to the .beta.-chain of HLA-DR. Claim 72 embodies the composition of claim 71, wherein said antigen-binding domain binds to an epitope of the first domain of the .beta.-chain of HLA-DR. Claim 73 embodies the composition of any of claims 66-69, wherein said cells are lymphoids cells. Claim 74 is drawn to the composition of any of claims 66-69, wherein said cells are non-lymphoid cells and express MHC class II antigens. Claim 75 embodies the composition of any of claims 66-69, having an IC.sub.50 for suppressing an immune response of 1 .mu.M or less. Claim 76 embodies the composition of any of claims 66-69, having an IC.sub.50 for inhibition of IL-2 secretion of 1 .mu.l M or less. Claim 77 embodies the composition of any of claims 66-69, having an IC.sub.50 for inhibiting T cell proliferation of 1 .mu.M or less. Claim 78 embodies the composition of any of claims 66-69, wherein said antigen-binding domain binds to one or more HLA-DR types selected from the group consisting of DR1-0101, DR2-15021, DR3-0301, DR4Dw4-0401, DR4Dw10-0402, DR4Dw14-0404, DR6-1302, DR6-1401, DR8-8031, DR9-9012, DRw53-B4*0101 and Drw52-B3*0101. Claim 79 embodies the composition of claim 78, wherein said antigen-binding domain binds to at least 5 different of said HLA-DR types. Claim 88 embodies the composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in down-regulation of expression of said antigen expressed on the surface of said cell. Claim 89 embodies the composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in inhibition of the interaction between said cell and other cells, wherein said interaction would normally lead to an immune response. Claim 90 embodies the composition of any one of claims 66-69, wherein said suppression of the immune response is brought about by or manifests itself in the killing of said cells. Claim 91 embodies he composition of claim 90, wherein said killing is mediated by binding of a plurality of antigen-binding domains, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor

immunological mechanisms are needed to causes or leads to said killing. Claim 92 embodies the composition of any one of claims 66-69, formulated in a pharmaceutically acceptable carrier and/or diluent. Claim 93 embodies the pharmaceutical preparation comprising the composition of claim 75 in an amount sufficient to suppress an immune response in an animal. Claim 94 is drawn to a pharmaceutical preparation comprising the composition of claim 76 in an amount sufficient to inhibit IL-2 secretion in an animal. Claim 95 is drawn to a pharmaceutical preparation comprising the composition of claim 77 in an amount sufficient to inhibit T cell proliferation in an animal.

Nagy et al disclose complete mAb, as well as bivalent and monovalent fragments of monoclonal antibodies, wherein said antibodies or fragments thereof bind to the HLA-DR molecule (page 4, lines 9-24, page 9, line 16- to page 10, line 23), thus fulfilling the specific embodiments of claims 33 drawn to F(ab)'2, claim 34, drawn to Fab and claim 35 drawn to IgG2a and IgG2b.. Nagy et al disclose that bivalent F(ab)'2 fragments and whole mAb are cytotoxic to B lymphocytes and because immunosuppression by the downregulation of the HLA-DR antigen, but the monovalent Fab fragments retain the ability to downregulate HLA-DR without the ability to cause cytotoxicity (page 1, lines 25-31, and page 4, line 32 to page 5, line 2). Nagy et al disclose that said antibodies can be identified by using the transformed human B-lymphoblastic cell line and assaying for dead cells in culture (page 6, lines 19-30, page 7, lines 11-19). Stedman's Medical dictionary defines "non-Hodgkin's lymphoma" and any other lymphoma that is not Hodgkin's lymphoma, thus the disclosure of the EBV-LCL cell lines fulfills the specific embodiments of claims 11. Nagy et al disclose Priess and LG2 cell lines as cell lines which react with antibodies having the desired properties of the invention, thus fulfilling the specific embodiments of claim 16. Nagy et al also disclose that the antibodies or fragments thereof cause downregulation of HLA-DR antigen on monocytic APC cells (page 22 lines 12-16), thus fulfilling the specific embodiment of claim 74 with regard to a non-lymphoid cell. Nagy et al disclose pan-DR specific mAb which bind to at least 5 different HLA-DR types fulfilling the specific embodiment of claim 79 (page 4, lines 11-14 and page 15). Nagy et al disclose the subtypes of DRB1*0101 thus fulfilling the specific embodiments of claims 20 and

78, with regard to DR1-0101. Nagy et al disclose that the ability to downregulate the HLA-DR antigen correlates to the recognition of epitopes located on the alpha 1 and beta 1 domains of the class II molecule (page 28, line 35 to page 29, line 2) thus fulfilling the specific embodiments of claims 18, 19, 71 and 72. Nagy et al discloses pharmaceutical preparations comprising the monovalent Fab fragment (claims 5-7), thus fulfilling the specific embodiments of 92, 93 and 95, in addition to the specific embodiments of claim 17, drawn to non-lymphoid cell, as an antigen-presenting cell (APC) include non-lymphoid cells. Nagy et al further disclose that the described antibodies can have multiple actions comprising elimination of antigen presenting cells by direct cytotoxicity, reduction of the available HLA-DR molecules on remaining viable APC by down regulation of cell surface expression and hindrance of class II MHC, thus fulfilling the specific embodiments of claims 88-90. With regard to the plurality of antigen-binding domains of claim 91, it is noted that the whole mAb as taught by Nagy et al would have 12 CDR regions, thus fulfilling the specific limitation of a plurality of antigen binding domains and the specific embodiment of claim 36 drawn to a multivalent polypeptide formed prior to binding a cell. Nagy et al disclose an IC(50) values for inhibition of T-cell response, wherein said values are in the nanoMolar range, thus fulfilling the specific embodiment of claims 75 and 77 drawn to Ic(50) values of less than 1 microMolar.

Abbas et al disclose in Table 7-3 that the expression of Il-2 by T-lymphocytes is more than 100-fold greater in activated cells. Thus, one of skill in the art would conclude that the pharmaceutical composition of claim 94 would inherently be the pharmaceutical composition as disclosed by Nagy as the inhibition of the T-cell response as taught by Nagy et al would inherently result in the inhibition of Il-2 secretion.

Drenou et al disclose that the cytotoxic action of anti-HLA-DR antibodies on B lymphocytes is due to an innate pre-programmed process of said cells results in death of said lymphocytes by a pathway that was not a classical apoptotic pathway in that it was caspase-independent, and did not exhibit the oligosomal DNA fragmentation typical of apoptotic cells. Drenou et al disclose that the cytotoxicity cannot be inhibited by zVAD-fmk or DEVD-fmk, thus the specific embodiments of claims 30-32 are inherent in the antibodies disclosed by Nagy et al.

With regard to claims 7-10, it appears that the antibodies disclosed by Nagy et al inherently have the limitations of claims 7-10, to the extent that claims 7-9 are dependent on claim 2. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 2, 7-11, 18-20, 30-37, 55, 56, 66, 71-78 and 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and

Molecular Immunology (text), 1991, page 165) in view of .Rheinnecker et al (Journal of Immunology, 1996, pp. 2989-2997)

The specific embodiments of claims 2, 7-11, 18-20, 30-36, 55, 56, 66, 71-78 and 88-95 and the teachings of Nagy et al as applied to the limitation of said claims are set forth above. Claim 37 is drawn to the composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed after binding to a cell.

Nagy et al teach composition of claim 2, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed prior to binding to a cell. Nagy et al d not teach a multivalent polypeptide that is formed after binding to a cell.

Rheinnecker et al teach a multivalent polypeptide that is formed after binding to a cell, wherein a "mini-antibodies" are assembled by means of human transcription factor 53 (page 2991, second column, lines 1-8). Rheinnecker et al teach that the binding of the tetrameric mini-antibody reaches a plateau with about 20 times more binding sites attached to the antigen at the end of the association phase in comparison to a Fab fragment (page 2996, first column bridging paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a mini-antibody by means of the tetramerization domain of p53, wherein said mini-antibody would bind to HLA-DR. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rheinnecker on the greater affinity of the tetrameric mini-antibodies for antigen in contrast to a Fab fragment.

18. Claims 2, 7-11, 18-20, 30-36, 55, 56, 66, 68, 69, 71-78 and 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and Molecular Immunology (text), 1991, page 165) in view of Winter et al (annu Rev Immunol, 1994, Vol. 12, pp. 433-455) and Engberg et al (Molecular biotechnology, 1996, Vol.6, pp. 287-

310) and Schlom (Monocloanl Antibodies: They're More and Less Than You Think, In: Molecular foundations of Oncology, 1991, pages 95-134).

Claim 68 is drawn to a composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a Kd of 1 .muM or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to human MHC class II antigen, wherein treating cells expressing MHC Class II with said polypeptide causes or leads to suppression of an immune response. Claim 69 is drawn to the composition of claim 68, wherein the method for isolating the antigen-binding domain includes the further steps of: a. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and b. isolation of VL and VH domains from the library of variants by ability to bind to human MHC class II antigen with a Kd of 1 .muM or less; c. (optionally) repeating steps (a) and (b) with at least one other of the CDR1, CDR2 and CDR3 sequences.

The compositions taught by Nagy et al inherently comprising all of the above limitations with the exception of an antigen-binding domain of human composition, and the isolation of said antibodies from a library of Vh and Vl clones.

Schlom teaches that it is an unrealistic expectation that just one or two administrations of a therapeutic agent could be effective, and that the anti-HAMA response that develops after multiple injections of murine mAb interferes with the ability of the antibody to target the antigen Schlom teaches humanized antibodies as a solution to overcoming the HAMA response (page 98, second column 24 to page 99, first column, line 4). Schlom teaches humanization as an alternative to human antibodies because (at the time of publication of Schlom (1991)) only a few human mAb made by hybridoma technology were available (page 97, first column, lines 4-27).

Winter et al teach that isolation of antibodies by means of phage display of human antibody fragments allows for the isolation of antibodies against self antigens (abstract).

Engberg et al teach the procedures for the expression and screening of libraries of human antibody fab fragments.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to screen a library of human Fab fragments for binding to the HLA-DR antigen as taught by Nagy et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom on the desirability of avoiding the anti-HAMA response and the teachings of Winter et al on the ability of isolating human antibody fragments which bind to human self antigens by means of phage display and the teachings of Engberg et al on the ease of screening antibody fragments of human origin by means of phage display.

19. Claims 1-7-11, 18-20, 30-36, 55, 56, 66, 68, 69, 71-78 and 88-95 rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and Molecular Immunology (text), 1991, page 165) and Engberg et al (Molecular biotechnology, 1996, Vol.6, pp. 287-310) as applied to claims 2, 7-11, 18-20, 30-36, 55, 56, 66, 68, 69, 71-78 and 88-95 above, and further in view of Winter et al (annu Rev Immunol, 1994, Vol. 12, pp. 433-455) and Ames et al (Journal of Immunological Methods, 1995, Vol. 184, pp. 177-186)..

Claim 1 is drawn to a composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. Claim 3 is drawn to a composition including a multivalent polypeptide comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing, wherein said antigen-binding domains individually bind to human HLA-DR with a Kd of 1 .muM or less. Claim 4 is drawn to a composition including a multivalent polypeptide

comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said cell killing, wherein said multivalent polypeptide has an EC.50 of 100 nM or less for killing activated lymphoid cells. Claim 5 is drawn to a composition including a polypeptide comprising at least one antibody-based antigen-binding domain that binds to human HLA-DR with a Kd of 1 .muM or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to at least one epitope of human HLA-DR, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. Claim 6 is drawn to a composition of claim 5, wherein the method for isolating the antigen-binding domain includes the further steps of: a. generating a library of variants of at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and b. isolation of VL and VH domains from the library of variants by ability to bind to human HLA-DR with a K.sub.d of 1 .muM or less.

The combination of Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and Molecular Immunology (text), 1991, page 165) and Engberg et al render obvious the compositions comprising a Fab fragment having an antigen-binding region of human origin for the reasons set forth above. None of the references teach a full length antibody or a bi-valent F(ab)'2 fragment. Nagy et al teach the full length antibody or the F(ab)2' fragment is necessary for the cytotoxic effect of the antibody as separated from the immunosuppressive effect.

Ames et al (Journal of Immunological Methods, 1995, vol. 184, pp. 177-186) teach how to convert Fab antibody isolated from phage display to full length immunoglobulins.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make full length antibodies out of human Fab fragments as taught

by Ames and Engbert et al and Winter et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Nagy et al on the induction of a cytotoxic effect from the binding of the bi-valent full length fragments versus the monovalent Fab fragments, an the further teachings of Ames et al on how to obtain full length human antibodies from human Fab fragments and the teachings of Engberg on the screening of human Fab libraries for binding to a target antigen and the teachings of Winter et al on the desirability of using phage display when a human antibody against a human self antigen is sought.

20. Claims 2, 7-11, 18-20, 30-37, 55, 56, 59-61, 66, 71-78 and 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over 2, 7-11, 18-20, 30-37, 55, 56, 66, 71-78 and 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy et al (WO 96/17874) as evidenced by Drenou et al (Journal of Immunology, October 1999, Vol. 163, pp. 4115-4124) and Abbas et al (Cellular and Molecular Immunology (text), 1991, page 165) in view of what is suggested in Nagy et al and the abstract of Ratech (Human Pathology, 1990, vol. 21, pp. 1275-1282).

Claim 56 embodies the diagnostic composition of claim 55, further comprising a cross-linking moiety or moieties. Claim 59 is drawn to a kit to identify patients that can be treated with a composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent comprising: a. a composition of any of claims 1-6; and b. means to measure the degree of killing or immunosuppression of said cells. Claim 60 is drawn to a kit comprising: a. a composition according to any one of claims 1-6, and b. a cross-linking moiety. Claim 61 is drawn to a kit comprising: a. a composition according to any one of claims 1-6, and b. a detectable moiety or moieties, and c. reagents and/or solutions to effect and/or detect binding of (a) to an antigen.

The combination of Nagy et al as evidenced by Drenou et al and Abbas et al render obvious the limitations of claims 2, 7-11, 18-20, 30-37, 55, 56, 66, 71-78 and 88-95 for the reasons set forth above. Nagy et al teach that cross linking of the HLA-DR receptor is required

for cytotoxicity. Nagy et al do not teach a diagnostic composition, a kit or a kit comprising a cross linking agent.

The abstract of Ratech teaches that malignant lymphomas of mixed cell type can be separated from other B cell lymphomas on the basis of HLA-DR distribution.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a diagnostic composition comprising a Fab fragment of an antibody which binds to the HLA-DR antigen as taught by Nagy et al and a cross linking agent for a diagnostic agent for the separation of B-cell malignant lymphomas of mixed cell type.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Nagy et al on the cytotoxic effect that would be expected after binding of Fab fragments which were then cross linked, and the teachings of the abstract of Ratech on the differences between HLA-DR density in b-cell lymphomas of the mixed cell type. One of skill in the art would know that the high density HLA-DR correlated with large cells will be more easily cross linked due to the higher antigen density, and the resulting cytotoxic effect observed after cross slinking would be indicative that the patient would respond to treatment with the anti-HLA-DR antibodies taught by Nagy et al.

21. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over any of Ishizuka et al (Cancer Research, 1998, Vol. 18, pp. 2513-2518) or Eray et al (International Immunology, 1994, Vol. 6, pp. 1817-1827) or Nakamura et al (Cancer Research, 1999, Vol. 59, pp. 5323-5330) or Kita et al (Biochemical and Biophysical Research Communications, 1996, Vol. 226, pp. 59-69) or Funakoshi et al (Blood, 1997, Vol. 90, pp. 3160-3166) or Vollmers et al (Oncology Reports, 1998, vol. 5, pp. 35-40) in view of Schlom (Monocloanl Antibodies: They're More and Less Than You Think, In: Molecular foundations of Oncology, 1991, pages 95-134) and Winter et al (annu Rev Immunol, 1994, Vol. 12, pp. 433-455) and Engberg et al (Molecular biotechnology, 1996, Vol.6, pp. 287-310) and Ames et al (Journal of Immunological Methods, 1995, vol. 184, pp. 177-186).

Ishizuka et al or Eray et al or Nakamura et al or Kita et al or Funakoshi et al or Vollmers et al teach murine monoclonal antibodies or humanized monoclonal antibodies, wherein said antibodies kill cells by means of apoptosis. Neither of the references teaches an antibody having an antigen-binding domain of human composition.

Schlom teaches that it is an unrealistic expectation that just one or two administrations of a anti-cancer therapeutic agent could be effective, and that the anti-HAMA response that develops after multiple injections of murine mAb interferes with the ability of the antibody to target the tumor. Schlom teaches humanized antibodies as a solution to overcoming the HAMA response (page 98, second column 24 to page 99, first column, line 4). Schlom teaches humanization as an alternative to human antibodies because (at the time of publication of Schlom (1991)) only a few human mAb made by hybridoma technology were available (page 97, first column, lines 4-27).

Engberg et al (Molecular biotechnology, 1996, Vol.6, pp. 287-310) teach the procedures for the expression and screening of libraries of human antibody fab fragments.

Ames et al (Journal of Immunological Methods, 1995, vol. 184, pp. 177-186) teach how to convert Fab antibody isolated from phage display to full length immunoglobulins.

Winter et al teach the desirability of using phage display when a human antibody against a human self antigen is sought.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute a human antibody, made by the methods taught in Engberg et al and Ames et al for the murine and humanized antibodies taught by Ishizuka et al or Eray et al or Nakamura et al or Kita et al or Funakoshi et al or Vollmers et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom on the desirability of avoiding the anti-HAMA response, the teachings of Winters et al on the ease of obtaining human antibody fragments which bind to human self antigens, and the teachings of Ames et al on the construction of bivalent antibodies from Fab antibodies obtained from recombinant libraries.

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

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